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09/784,674	02/15/2001	Karen W. Shannon	10971464-3	3167

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EXAMINER	
NEGIN, RUSSELL SCOTT	

ART UNIT	PAPER NUMBER
1631	

NOTIFICATION DATE	DELIVERY MODE
10/22/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

IPOPS.LEGAL@agilent.com

Office Action Summary	Application No.	Applicant(s)
	09/784,674	SHANNON ET AL.
	Examiner	Art Unit
	Russell S. Negin	1631

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on 30 July 2007.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex partè Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1,2,5-25,27-40 and 102-165 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1,2,5,6,8-13,15-24,30-32,37,39,40,102-117,119-136 and 139-165 is/are rejected.

7)☒ Claim(s) 6,7,14,25,27-29,33-36,38,118,137,138 and 148 is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.

4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

5) ☐ Notice of Informal Patent Application

6) ☐ Other: _____.

DETAILED ACTION

Comments

Applicants' amendments and request for reconsideration in the communication filed on 30 July 2007 are acknowledged and the amendments are entered.

Claims 1, 2, 5-25, 27-40, and 102-165 are pending and examined in this Office action.

Claim Objections

Claims 6 and 148 are objected to because of the following informalities:

Claim 6 recites, "A method according to claim I..."

Claim 148 recites the term "oligonuc1eotides" in line 8.

Appropriate correction is required.

Claims 7, 14, 25, 27-29, 33-36, 38, 118, and 137-138 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claim Rejections - 35 USC § 112

The rejections of claims 1-2, 5-25, 27-40, 104, 116-117, 124, 151, and 160 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out

and distinctly claim the subject matter which applicant regards as the invention are withdrawn in view of amendments made by applicant to the set of claims filed on 30 July 2007.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

35 U.S.C. 103 Rejection #1, #2, #3, and #5 are reiterated from the previous Office action while Rejection #4 is newly applied:

35 U.S.C. 103 Rejection #1:

Claims 1, 10, 15, 16-22, 37, 39-40, 122, 124, 126-132, and 139-145 are rejected under 35 U.S.C. 103(a) as being unpatentable over Southern et al. [Nucleic Acids Research, 1994, volume 22, pages 1368-1373] in view of Southern [Current Opinion in Biotechnology, 1996, volume 7, pages 85-88] in view of Drmanac et al. [Genomics, volume 4, pages 114-128, 1989].

Claims 1 and 122 are independent claims drawn to computer based methods of selecting a hybridization oligonucleotide to hybridize to a target nucleotide sequence. They involve examining and/or clusters of oligonucleotides in order to predict hybridization efficiencies.

Claim 1 has the feature of using staggered nucleotide sequences, each of the same length.

Claim 122 has the feature of using nucleotide sequences, each of the same length.

The article of Southern et al. (1994), states in its abstract, "Arrays of oligonucleotides corresponding to a full set of complements of a known sequence can be made in a single series of base couplings in which each base in the complement is added in turn."

Figure 1 on page 1369 of Southern et al. (1994) illustrates an array of oligonucleotides schematically. (as recited in part of step a in claims 1 and 22)

Figures 3 and 4 of Southern et al. (1994) illustrate the experimental and computational analysis of the results on pages 1371 and 1372, respectively. The

parameter in Figure 3c indicating extent of hybridization is the color of each ring with respect to the others (i.e., a darker rung represents greater hybridization intensity). This "rung darkness" represents a parameter of hybridization intensity (as recited in step b of claims 1 and 122). Based on this parameter, several clusters of darker colors are present in Figure 3c. Figure 3c also illustrates (through numbers with arrows) selection and identification of specific oligonucleotides in the subsets that are hybridizable to the target nucleotide sequences (as recited in claims 123 and steps c, d, e, and f of claims 1 and 22). In Figure 3c, the parameter that is being evaluated is the darkness of the rings (as recited in claim 10).

As is stated in the caption to Figure 3 on page 1371 of Southern et al. (1994):

> Figure 3. Hybridisation of an oligopyrimidine and a RNA to scanning arrays. a. Hybridisation of a sequence of pyrimidines,... to an arrays of complementary oligopurines based on the sequence,... b. Hybridisation of a 528-base transcript of exon 10 of the CFTR gene to an array representing bases 287-305,... In both experiments, the reaction cell was 30 nm diameter and the offset 3 mm, giving rise to decanucleotides along the center line. c. The hybridization pattern shown in 3b has unexpected features. Coupling started on the right of the plate, so the bases in the crescent shape at position 2 are the dinucleotide GG; adding a T in the third position abolishes the 'hybridisation' of the target. Further along the plate, it can be seen that a shift of one position along the sequence can cause a fall from strong to negligible interaction, and in one position, the 7-, 8- and 9-mers all interact more strongly that the 10-mer.

Consequently, the caption and its illustration indicates qualitative ranking between cluster based on both cluster size and lengths of oligonucleotides within the clusters. Subsets of the clusters are selected with the numbered arrows above the picture. The oligonucleotides can be DNA or RNA and they are parts of microarrays as indicated in the title of Southern et al. (1994) and the first column of page 1373 of Southern et al. (1994).

However, Southern et al. (1994) does not teach the step of predicting the hybridization of the oligonucleotide by the presence of said hybridization cluster. In addition, Southern (1994) does not teach sequential overlapping oligomers of equal length. (as recited in part of step a of independent claims 1, 102, 122, and 148).

Southern (1996), entitled, "High density gridding: techniques and applications," states in the section, "Dedicated oligonucleotide arrays for mutation analysis" on page 87, column 2, lines 4-7, "It is envisaged that dedicated arrays will be useful for mutation detection. Comparison of the hybridization patterns of wild-type and mutant sequences to an array of oligonucleotides complementary to the wild type will reveal a difference." (as recited in part of step e of instant claims 1 and 122).

The abstract of Southern (1996) states:

> Much progress has been made in the development of techniques for constructing dense grids either of ligands, such as peptides and oligonucleotides, or of cloned nucleic acids. Such arrays are finding practical applications in the analysis of sequence variation and gene expression. Methods for carrying out large numbers of analyses in parallel will be essential for the genetic programme that is developing from large-scale sequencing projects.

Southern (1994) does not teach sequential overlapping oligomers of equal length.

The article of Drmanac et al, entitled, "Sequencing of megabase plus DNA by hybridization: theory of the method," states in the abstract that a similar type of staggered DNA analysis is employed as in the Southern references (i.e. see Figure 1), but now the method is theoretical rather than experimental and computer power is necessary. As stated in lines 1-4 and 30-35 of the abstract:

> A mismatch-free hybridization of oligonucleotides containing from 11 to 20 monomers to unknown DNA represents, in essence, a sequencing of a complementary target...

> The sequence can be derived from simple primary data only by extensive computing. Phased experimental tests and computer simulation increasing in complexity are needed before accurate estimates can be made...

Figure 1 of Drmanac on page 115 illustrates the target sequence (Figure 1A) and the sequential overlapping 8-mers (Figure 1B) which hybridize to the target and assist in sequencing it. (as recited in part of step c of independent claims 1 and 122).

It would have been obvious to someone of ordinary skill in the art at the time of the instant invention to modify the complementary arrays of Southern et al. (1994) with the mutation detection method of Southern (1996) with the empirical and computational method of detecting hybridization of Drmanac et al., because while all methods use the same method of staggered hybridization and the Southern (1996) cites the Southern et al. (1994) as its method of use, Southern (1996) has the advantage of employing the techniques of Southern et al. (1994) for mutation analysis and Drmanac et al. has the advantage of examining hybridization both empirically and computationally for more accurate sequence detection.

It would be further obvious to conduct the methods of Southern et al. (1994), Southern (1996) and Drmanac et al. within computers as it is obvious to automate a manual activity. The MPEP states:

> In re Venner, 262 F.2d 91, 95, 120 USPQ 193, 194 (CCPA 1958) (Appellant argued that claims to a permanent mold casting apparatus for molding trunk pistons were allowable over the prior art because the claimed invention combined "old permanent-mold structures together with a timer and solenoid which automatically actuates the known pressure valve system to release the inner core after a predetermined time has elapsed." The court held that broadly providing an automatic or mechanical means to replace a manual activity which accomplished the same result is not sufficient to distinguish over the prior art.).

Claim 10 is dependent from claim 1 with the additional limitation of generating probabilities of hybridization based on mathematical transformations.

The appendix of Drmanac et al. lists such equations- specifically equation 1 on page 122 illustrates such a probability.

Claims 15 and 129 are dependent from claims 1 and 129 with the additional limitation of using a computer program.

As stated above with regards to In re Venner, it is obvious to automate a manual activity.

Claims 16-22 and 130-132 depend from claims 1 and 122 with the extra limitation of claiming the species of oligonucleotide and target molecule (i.e. DNA, RNA, labeled oligonucleotide, or attached to a surface).

Southern (1994) recites both DNA, RNA and modified oligonucleotides at the bottom of column 2 on page 1369.

Claims 37, 39, 40 and 139-141 depend from claims 1 and 122 with the extra limitation of claiming certain types and properties of clusters.

Figure 3 of Southern (1994) illustrates clusters along adjacent regions of the oligonucleotide. Cluster sizes in Figure 3c include counting the size of contiguous nucleotides and the number of based that begin each region of the oligonucleotide.

Claims 124 and 126-128 depend from claim 122 with the extra limitation of claiming specific types of cluster ranking and properties of the clusters.

The article of Drmanac et al, entitled, "Sequencing of megabase plus DNA by hybridization: theory of the method," states in the abstract that a similar type of staggered DNA analysis is employed as in the Southern references (i.e. see Figure 1), but now the method is theoretical rather than experimental and computer power is necessary. As stated in lines 1-4 and 30-35 of the abstract:

> A mismatch-free hybridization of oligonucleotides containing from 11 to 20 monomers to unknown DNA represents, in essence, a sequencing of a complementary target...
> The sequence can be derived from simple primary data only by extensive computing. Phased experimental tests and computer simulation increasing in complexity are needed before accurate estimates can be made...

Figure 1 of Drmanac on page 115 illustrates the target sequence (Figure 1A) and the sequential overlapping 8-mers (Figure 1B) which hybridize to the target and assist in sequencing it.

Claims 142 and 144 are dependent from claim 102 and 122 with the additional limitation that the method is under computer control.

As stated above with regards to In re Venner, it is obvious to automate a manual activity.

Claims 143 and 145 are dependent from claims 142 and 144 with the additional limitation that the sequences are electronically transferred to a manufacturing system.

As stated above with regards to In re Venner, it is obvious to automate a manual activity. Manufacturing via automated electrical signals is a type of automated activity.

Response to Arguments:

Applicant's arguments filed 30 July 2007 have been fully considered but they are not persuasive.

Applicant's arguments concerning this rejection are on pages 21-24 of the Remarks.

Applicant asserts that each of the references used in this obviousness prior art rejection are empirical and do not employ a computer to execute the method. This is not found to be persuasive because it is obvious to automate a manual activity (see the quote from the MPEP regarding In re Venner above).

35 U.S.C. 103 Rejection #2:

Claims 2, 11-13, 102-104, 106-112, 119-121, 123, 146-151, and 153-156 are rejected under 35 U.S.C. 103(a) as being unpatentable over Southern et al. (1994) in view of Southern (1996) in view of Drmanac et al. as applied to claims 1, 10, 15, 16-22, 37, 39-40, 122, 124, 126-132, and 139-145 above, and further in view of Southern et al. [Genomics, 1992, volume 13, pages 1008-1017].

Claim 2 is dependent from claim 1 with the additional limitation of ranking said oligonucleotides based on the number in said clusters.

Claim 11 is dependent from claim 1 with the additional limitation of ranking said oligonucleotides based on the number in said clusters and selecting a subset of said clustered oligonucleotides.

Claim 12 depends from claim 11 with the additional limitation of said subset comprises any number of oligonucleotides within said cluster.

Claim 13 claims statistically sampling a cluster of oligonucleotides.

Southern et al. (1994) in view of Southern (1996) in view of Drmanac et al. as applied to claims 1, 10, 15, 16-22, 37, 39-40, 122, 124, 126-132, and 139-145 above do not teach the method of quantitative ranking as required by the instant claims.

The article of Southern et al. (1992), entitled, "Analyzing and comparing nucleic acid sequences by hybridization to arrays of oligonucleotides: evaluation using experimental models," illustrates on page 1013 in Tables I and II ranks of clusters illustrated in Figure 5 on page 1013 of Southern et al. (1992) ranks and dimensionless scores of sequences within each cluster.

It would have been obvious at the time of the instant invention to modify Southern et al. (1994) in view of Southern (1996) in view of Drmanac et al. as applied to claims 1, 10, 15, 16-22, 37, 39-40, 122, 124, 126-132, and 139-145 above, in further view of Southern et al. (1992) to result in the instant invention because Southern (1992) has the advantage of quantitative ranking for more efficient genomic analysis.

Claims 102 and 148 are drawn to a computer based method for selecting a hybridization oligonucleotide to hybridize to a target nucleotide sequence. This claim contains all of the elements of claim 122 with the additional embodiment of ranking the oligonucleotides.

The article of Southern et al. (1992), entitled, "Analyzing and comparing nucleic acid sequences by hybridization to arrays of oligonucleotides: evaluation using experimental models," illustrates on page 1013 in Tables I and II ranks of clusters illustrated in Figure 5 on page 1013 of Southern et al. (1992) ranks and dimensionless scores of sequences within each cluster.

Claims 103-104 and 106-108 depend from claim 102 with the extra limitation of claiming specific types of cluster ranking and properties of the clusters.

The article of Drmanac et al, entitled, "Sequencing of megabase plus DNA by hybridization: theory of the method," states in the abstract that a similar type of staggered DNA analysis is employed as in the Southern references (i.e. see Figure 1), but now the method is theoretical rather than experimental and computer power is necessary. As stated in lines 1-4 and 30-35 of the abstract:

> A mismatch-free hybridization of oligonucleotides containing from 11 to 20 monomers to unknown DNA represents, in essence, a sequencing of a complementary target...
> The sequence can be derived from simple primary data only by extensive computing. Phased experimental tests and computer simulation increasing in complexity are needed before accurate estimates can be made...

Figure 1 of Drmanac on page 115 illustrates the target sequence (Figure 1A) and the sequential overlapping 8-mers (Figure 1B) which hybridize to the target and assist in sequencing it.

Claim 109 depends from claim 102 with the additional limitation of using a computer program.

As stated above with regards to In re Venner, it is obvious to automate a manual activity.

Claims 110-112 depend from claim 102 with the extra limitation of claiming the species of oligonucleotide and target molecule (i.e. DNA, RNA, labeled oligonucleotide, or attached to a surface).

Southern (1994) recites both DNA, RNA and modified oligonucleotides at the bottom of column 2 on page 1369.

Claims 119-121 depend from claim 102 with the extra limitation of claiming certain types and properties of clusters.

Figure 3 of Southern (1994) illustrates clusters along adjacent regions of the oligonucleotide. Cluster sizes in Figure 3c include counting the size of contiguous nucleotides and the number of based that begin each region of the oligonucleotide.

Claim 123 is dependent from claim 122 with the additional limitation of ranking said oligonucleotides based on the number in said clusters.

The article of Southern et al. (1992), entitled, “Analyzing and comparing nucleic acid sequences by hybridization to arrays of oligonucleotides: evaluation using experimental models,” illustrates on page 1013 in Tables I and II ranks of clusters illustrated in Figure 5 on page 1013 of Southern et al. (1992) ranks and dimensionless scores of sequences within each cluster.

Claim 146 is drawn to a computer system for conducting a method for selecting a hybridization oligonucleotide to hybridize to a target nucleotide sequence with a means for conducting each step dictated in claim 102 (including ranking).

Southern et al. (1994) in view of Southern (1996) in view of Drmanac et al. as applied to claims 1, 10, 15, 16-22, 37, 39-40, 122, 124, 126-132, and 139-145 above do not teach the apparatus of statistical sampling with dimensionless numbers as required by the instant claims.

The article of Southern et al. (1992), entitled, "Analyzing and comparing nucleic acid sequences by hybridization to arrays of oligonucleotides: evaluation using experimental models," illustrates on page 1013 in Tables I and II ranks of clusters illustrated in Figure 5 on page 1013 of Southern et al. (1992) ranks and dimensionless scores of sequences within each cluster.

Claim 147 is dependent from claim 146 with the additional limitation that the identified subset is electronically transferred to an oligonucleotide array manufacturing system.

As stated above with regards to In re Venner, it is obvious to automate a manual activity. Manufacturing via automated electrical signals is a type of automated activity.

Claims 149-151 depend from claim 148 with the extra limitation of claiming specific types of cluster ranking and properties of the clusters.

The article of Drmanac et al, entitled, "Sequencing of megabase plus DNA by hybridization: theory of the method," states in the abstract that a similar type of staggered DNA analysis is employed as in the Southern references (i.e. see Figure 1), but now the method is theoretical rather than experimental and computer power is necessary. As stated in lines 1-4 and 30-35 of the abstract:

> A mismatch-free hybridization of oligonucleotides containing from 11 to 20 monomers to unknown DNA represents, in essence, a sequencing of a complementary target...
> The sequence can be derived from simple primary data only by extensive computing. Phased experimental tests and computer simulation increasing in complexity are needed before accurate estimates can be made...

Figure 1 of Drmanac on page 115 illustrates the target sequence (Figure 1A) and the sequential overlapping 8-mers (Figure 1B) which hybridize to the target and assist in sequencing it.

Claim 153 depends from claim 148 with the additional limitation of using a computer program.

As stated above with regards to In re Venner, it is obvious to automate a manual activity.

Claims 154-156 depend from claim 148 with the extra limitation of claiming the species of oligonucleotide and target molecule (i.e. DNA, RNA, labeled oligonucleotide, or attached to a surface).

Southern (1994) recites both DNA, RNA and modified oligonucleotides at the bottom of column 2 on page 1369.

Response to Arguments:

Applicant's arguments filed 30 July 2007 have been fully considered but they are not persuasive.

Applicant's arguments concerning this rejection are on pages 24-28 of the Remarks.

Applicant asserts that each of the references used in this obviousness prior art rejection are empirical and do not employ a computer to execute the method. In other words, the addition of the Southern et al. (1992) reference did not cure the deficiencies of the previous references. This is not found to be persuasive because it is obvious to automate a manual activity (see the quote from the MPEP regarding In re Venner above).

35 U.S.C. 103 Rejection #3:

Claims 5, 6, 23-24, 30-32, 105, 125, 133-136, 157, and 159-165 are rejected under 35 U.S.C. 103(a) as being unpatentable over Southern et al. (1994) in view of Southern (1996) in view of Drmanac et al. as applied to claims 1, 10, 15, 16-22, 37, 39-40, 122, 124, 126-132, and 139-145 above, and further in view of Petersheim et al. [Biochemistry, 1983, volume 22, pages 256-263].

Claim 5 is dependent from claim 1 in which a thermodynamic or kinetic factor is selected as a parameter.

Claim 6 is dependent from claim 1 with the additional limitation that a composition factor is chosen from (G+C) content.

Claim 23 is dependent from claim 1 with the additional limitation that for each oligonucleotide/target nucleotide duplex, the difference between the predicted duplex melting temperature and the temperature of hybridization is chosen.

Southern et al. (1994) in view of Southern (1996) in view of Drmanac et al. as applied to claims 1, 10, 15, 16-22, 37, 39-40, 122, 124, 126-132, and 139-145 above do not teach the thermodynamic parameters and cut-off values present in the instant claims.

The article of Petersheim et al, entitled, "Base-stacking and base-pairing contributions to helix stability: thermodynamics of double-helix formation with CCGG, CCGGp, CCGGAp, ACCGGp, CCGGUp, and ACCGGUp," states in the first sentence of the introduction, "Due to development of rapid sequencing techniques, there has been an explosion in our knowledge of nucleic acid sequences. This understanding provides a foundation for understanding the functions and mechanisms of these macromolecules."

Equations 1 through 5 on page 257 of Petersheim et al. provide the guidelines behind the thermodynamic parameters (free energy, melting temperature, entropy, and enthalpy) of duplex formation shown in Figures 2-6 on page 258-259 of Petersheim et al.

Consequently, thermodynamic parameters, including the G+C content of the sequences listed are examined, and duplex formation parameters.

It would have been obvious at the time of the instant invention to modify Southern et al. (1994) in view of Southern (1996) in view of Drmanac et al. as applied to

claims 1, 10, 15, 16-22, 37, 39-40, 122, 124, 126-132, and 139-145 above, in further view of Petersheim et al. to result in the instant invention because Petersheim et al. has the advantage of using thermodynamics to analyze structure and function of the same types of duplexes employed in the microarrays of Southern et al. It would have been further obvious to employ the ranges shown in the claims, as the hybridization process is analogous for oligonucleotides of any given length and location.

Claim 24 is dependent from claim 1 with the additional limitation that a cut-off value is established for each thermodynamic parameter.

Figure 2 et al. of Petersheim et al. displays in a sigmoidal curve the cutoff parameters for melting point (i.e. the ranges at which no conformational transitions occur).

Claim 30 is dependent from claim 1 with the additional limitation that two parameters are determined with at least one of the parameters being an association free energy.

Equations 1 through 5 on page 257 of Petersheim et al. provide the guidelines behind the thermodynamic parameters (free energy, melting temperature, entropy, and enthalpy) of duplex formation shown in Figures 2-6 on page 258-259 of Petersheim et al.

Claim 31 is dependent from claim 30 wherein the subsequence is 3-9 nucleotides in length.

Claim 32 is dependent from claim 30 wherein the subsequence is 5-7 nucleotides in length.

The sequences listed in the title of Petersheim et al. (CCGG, CCGGp, CCGGAp, ACCGGp, CCGGUp, and ACCGGUp) fulfill this requirement.

Claims 125 and 152 dependent from claims 122 and 148 in which a thermodynamic or kinetic factor is selected as a parameter.

Equations 1 through 5 on page 257 of Petersheim et al. provide the guidelines behind the thermodynamic parameters (free energy, melting temperature, entropy, and enthalpy) of duplex formation shown in Figures 2-6 on page 258-259 of Petersheim et al.

Claim 133 is dependent from claim 122 with the additional limitation that a cut-off value is established for each thermodynamic parameter.

Figure 2 et al. of Petersheim et al. displays in a sigmoidal curve the cutoff parameters for melting point (i.e. the ranges at which no conformational transitions occur).

Claim 134 is dependent from claim 122 with the additional limitation that two parameters are determined with at least one of the parameters being an association free energy.

Equations 1 through 5 on page 257 of Petersheim et al. provide the guidelines behind the thermodynamic parameters (free energy, melting temperature, entropy, and enthalpy) of duplex formation shown in Figures 2-6 on page 258-259 of Petersheim et al.

Claim 135 is dependent from claim 30 wherein the subsequence is 3-9 nucleotides in length.

Claim 136 is dependent from claim 30 wherein the subsequence is 5-7 nucleotides in length.

The sequences listed in the title of Petersheim et al. (CCGG, CCGGp, CCGGAp, ACCGGp, CCGGUp, and ACCGGUp) fulfill this requirement.

Claim 157 is drawn to a computer based method for selecting a hybridization oligonucleotide to hybridize to a target nucleotide sequence with the additional limitation of incorporating specific thermodynamic parameters into the claim (i.e. GC content, coupling efficiencies, mathematical transformations, and duplex melting temperatures).

Southern et al. (1994) in view of Southern (1996) in view of Drmanac et al. as applied to claims 1, 10, 15, 16-22, 37, 39-40, 122, 124, 126-132, and 139-145 above

do not teach the thermodynamic parameters and cut-off values present in the instant claims.

The article of Petersheim et al, entitled, “Base-stacking and base-pairing contributions to helix stability: thermodynamics of double-helix formation with CCGG, CCGGp, CCGGAp, ACCGGp, CCGGUp, and ACCGGUp,” states in the first sentence of the introduction, “Due to development of rapid sequencing techniques, there has been an explosion in our knowledge of nucleic acid sequences. This understanding provides a foundation for understanding the functions and mechanisms of these macromolecules.”

Equations 1 through 5 on page 257 of Petersheim et al. provide the guidelines behind the thermodynamic parameters (free energy, melting temperature, entropy, and enthalpy) of duplex formation shown in Figures 2-6 on page 258-259 of Petersheim et al.

Consequently, thermodynamic parameters, including the G+C content of the sequences listed are examined, and duplex formation parameters.

Claims 159-162 depend from claim 157 with the extra limitation of claiming specific types of cluster ranking and properties of the clusters.

The article of Drmanac et al, entitled, “Sequencing of megabase plus DNA by hybridization: theory of the method,” states in the abstract that a similar type of staggered DNA analysis is employed as in the Southern references (i.e. see Figure 1),

but now the method is theoretical rather than experimental and computer power is necessary. As stated in lines 1-4 and 30-35 of the abstract:

> A mismatch-free hybridization of oligonucleotides containing from 11 to 20 monomers to unknown DNA represents, in essence, a sequencing of a complementary target...
> The sequence can be derived from simple primary data only by extensive computing. Phased experimental tests and computer simulation increasing in complexity are needed before accurate estimates can be made...

Figure 1 of Drmanac on page 115 illustrates the target sequence (Figure 1A) and the sequential overlapping 8-mers (Figure 1B) which hybridize to the target and assist in sequencing it.

Claim 163 depends from claim 157 with the additional limitation of using a computer program.

As stated above with regards to In re Venner, it is obvious to automate a manual activity.

Claims 164-165 depend from claim 157 with the extra limitation of claiming the species of oligonucleotide and target molecule (i.e. DNA, RNA, labeled oligonucleotide, or attached to a surface).

Southern (1994) recites both DNA, RNA and modified oligonucleotides at the bottom of column 2 on page 1369.

Response to Arguments:

Applicant's arguments filed 30 July 2007 have been fully considered but they are not persuasive.

Applicant's arguments concerning this rejection are on pages 24-28 of the Remarks.

Applicant asserts that each of the references used in this obviousness prior art rejection are empirical and do not employ a computer to execute the method. In other words, the addition of the Petersheim et al. reference did not cure the deficiencies of the previous references. This is not found to be persuasive because it is obvious to automate a manual activity (see the quote from the MPEP regarding In re Venner above).

35 U.S.C. 103 Rejection #4:

Claims 105, 113-115, and 158 are rejected under 35 U.S.C. 103(a) as being unpatentable over Southern et al. (1994) in view of Southern (1996) in view of Drmanac et al. in view of Southern et al. (1992) as applied to claims 2, 11-13, 102-104, 106-112, 119-121, 123, 146-151, and 153-156 above, and further in view of Petersheim et al.

Claim 105 is dependent from claim 102 in which a thermodynamic or kinetic factor is selected as a parameter.

Southern et al. (1994) in view of Southern (1996) in view of Drmanac et al. in view of Southern et al. (1992) as applied to claims 2, 11-13, 102-104, 106-112, 119-121, 123, 146-151, and 153-156 above do not teach the thermodynamic parameters and cut-off values present in the instant claims.

The article of Petersheim et al, entitled, "Base-stacking and base-pairing contributions to helix stability: thermodynamics of double-helix formation with CCGG,

CCGGp, CCGGAp, ACCGGp, CCGGUp, and ACCGGUp," states in the first sentence of the introduction, "Due to development of rapid sequencing techniques, there has been an explosion in our knowledge of nucleic acid sequences. This understanding provides a foundation for understanding the functions and mechanisms of these macromolecules."

Equations 1 through 5 on page 257 of Petersheim et al. provide the guidelines behind the thermodynamic parameters (free energy, melting temperature, entropy, and enthalpy) of duplex formation shown in Figures 2-6 on page 258-259 of Petersheim et al.

Consequently, thermodynamic parameters, including the G+C content of the sequences listed are examined, and duplex formation parameters.

It would have been obvious at the time of the instant invention to modify Southern et al. (1994) in view of Southern (1996) in view of Drmanac et al. in view of Southern et al. (1992) as applied to claims 2, 11-13, 102-104, 106-112, 119-121, 123, 146-151, and 153-156 above in further view of Petersheim et al. to result in the instant invention because Petersheim et al. has the advantage of using thermodynamics to analyze structure and function of the same types of duplexes employed in the microarrays of Southern et al. It would have been further obvious to employ the ranges shown in the claims, as the hybridization process is analogous for oligonucleotides of any given length and location.

Claim 113 is dependent from claim 102 with the additional limitation that a cut-off value is established for each thermodynamic parameter.

Figure 2 et al. of Petersheim et al. displays in a sigmoidal curve the cutoff parameters for melting point (i.e. the ranges at which no conformational transitions occur).

Claim 114 is dependent from claim 102 with the additional limitation that two parameters are determined with at least one of the parameters being an association free energy.

Equations 1 through 5 on page 257 of Petersheim et al. provide the guidelines behind the thermodynamic parameters (free energy, melting temperature, entropy, and enthalpy) of duplex formation shown in Figures 2-6 on page 258-259 of Petersheim et al.

Claim 115 is dependent from claim 114 wherein the subsequence is 3-9 or 5-7 nucleotides in length.

The sequences listed in the title of Petersheim et al. (CCGG, CCGGp, CCGGAp, ACCGGp, CCGGUp, and ACCGGUp) fulfill this requirement.

Claim 158 is dependent from claim 1578 with the additional limitation of including ranking oligonucleotides.

The article of Southern et al. (1992), entitled, "Analyzing and comparing nucleic acid sequences by hybridization to arrays of oligonucleotides: evaluation using

experimental models," illustrates on page 1013 in Tables I and II ranks of clusters illustrated in Figure 5 on page 1013 of Southern et al. (1992) ranks and dimensionless scores of sequences within each cluster.

Response to Arguments:

This is a new rejection and therefore there are no arguments regarding this rejection in the Remarks.

35 U.S.C. 103 Rejection #5:

Claims 8-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Southern et al. (1994) in view of Southern (1996) in view of Drmanac et al. as applied to claims 1, 10, 15, 16-22, 37, 39-40, 122, 124, 126-132, and 139-145 above, and further in view of McMahon et al. [US Patent 5,310,650].

Claims 8 and 9 claim kinetic properties and coupling efficiencies of the hybridizations.

Southern et al. (1994) in view of Southern (1996) in view of Drmanac et al. as applied to claims 1, 10, 15, 16-22, 37, 39-40, 122, 124, 126-132, and 139-145 above do not teach the kinetic properties and coupling efficiencies of the reactions.

The invention of McMahon et al, entitled, "Method and device for improved reaction kinetics in nucleic acid hybridizations," teaches kinetics and coupling efficiencies of hybridizations in column 13 (Table 1) for improved binding assays.

It would have been obvious at the time of the instant invention to modify Southern et al. (1994) in view of Southern (1996) in view of Drmanac et al. as applied to claims 1, 10, 15, 16-22, 37, 39-40, 122, 124, 126-132, and 139-145 above in further view of McMahon et al. because McMahon et al. applies to hybridizations methods the use and study of both kinetics and hybridization efficiencies from a more efficient and improved assay.

Response to Arguments:

Applicant's arguments filed 30 July 2007 have been fully considered but they are not persuasive.

Applicant's arguments concerning this rejection are on pages 28-29 of the Remarks.

Applicant asserts that each of the references used in this obviousness prior art rejection are empirical and do not employ a computer to execute the method. In other words, the addition of the McMahon et al. reference did not cure the deficiencies of the previous references. This is not found to be persuasive because it is obvious to automate a manual activity (see the quote from the MPEP regarding In re Venner above).

Conclusion

No claim is allowed.

Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the

central PTO Fax Center. The faxing of such pages must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CFR § 1.6(d)). The Central PTO Fax Center Number is (571) 273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Russell Negin, Ph.D., whose telephone number is (571) 272-1083. The examiner can normally be reached on Monday-Friday from 7am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's Supervisor, Marjorie Moran, Supervisory Patent Examiner, can be reached at (571) 272-0720.

Information regarding the status of the application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information on the PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

10/12/07
RSN
12 October 2007

/Shubo (Joe) Zhou/

SHUBO (JOE) ZHOU, PH.D.
PRIMARY EXAMINER